Chemical Tools to Study Protein Prenylation

Protein lipid-modification involves the attachment of hydrophobic groups to polypeptides within cells after they are synthesized by ribosomes. The purpose of these modifications is to anchor specific proteins to the cell membrane where they can relay chemical messages from the exterior to the cellular interior. Protein prenylation is one example of lipid modification and consists of the addition of either C_{15} or C_{20} isoprenoid groups to a variety of proteins; such proteins play key roles in regulating processes within cells including cell division, shape, differentiation and memory. Of particular note is the observation that protein prenylation is required for the transforming activity of mutant Ras oncoproteins; inhibition of the enzyme farnesyltransferase (which catalyzes protein prenylation) arrests the growth of transformed cells in a variety of models. A number of inhibitors of this enzyme and others in the protein prenylation pathway are currently in clinical trials for cancer therapy and other diseases. This presentation will describe the use of chemical tools to and how they have been to probe the biology of protein prenylation as well as streamline the development of new protein-based therapeutics. New methodology for the synthesis of peptide libraries has enabled the specificity of prenyltransferases to be probed in detail and illuminated new types of proteins that may carry this modification. Synthetic isoprenoid probes have been used to identify prenylated proteins in a range of systems ranging from the malaria parasite to human cancer cells. New photoremovable protecting groups for thiols, that can be activated via two photon excitation, have been used to trigger or inhibit protein lipid modification in living cells. Ultimately, new discoveries from these fundamental studies should reveal new targets and strategies for therapeutic applications.